DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
ORA OPQO HQ, Room #2032 12420 Parklawn Drive, Rockville, MD 20857 ORAPHARMInternational483responses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	01/20/2020 - 01/24/2020
	FEI NUMBER 3010164491

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Vivek Gupta, Senior Vice President - Operations

FIRM NAME	STREET ADDRESS
Biocon Limited	Biocon Sez Plot No. 3, Phase Iv, Bommasandra-Jigani Link Road
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Bommasandra Post, Bangalore, Karnataka, 560099, India	Active Pharmaceutical Ingredients Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

1. Cleaning Validation Protocols designed to assess potential product-to-product carryover in non-dedicated, are not adequately performed. Specifically,

Per SOP No. QA/SOP/016, "Cleaning Validation", the "total carryover should be calculated based on swab result". Cleaning Validation Protocols are product specific and define the process, procedures, materials and documentation requirements. During execution of the cleaning validations, the performed cleaning actions are documented on the respective "Equipment Cleaning Checklist", while details of samples are documented on the "Technical Information Sheet for Equipment Cleaning Sample". However, neither the "Equipment Cleaning Checklist" or "Technical Information Sheet for Equipment Cleaning Sample", document the diluent used in the swab sample collection preparation, volume of diluent, or total area swabbed, as required by the respective protocol and SOP No. QA/SOP/016.

2. Failure to perform adequately investigate non-conformances. Specifically

Investigations into Out-of-Specification impurities test results, failed to assess the potential impact of (b) (4) (b) (4) settings during (b) (4) The (b) (4) parameters established as critical process parameters were not documented within production batch records prior to implementation of change control Ref No. BP1CCF-PC/19/040, which has a tentative closure date of March 31st, 2020. Per written procedure SOP No. QA/SOP/057, "Out-of-specification Procedure For Nonconforming Materials and Products/Batch Failures", Version 17, "When the evidence of laboratory error remains unclear or assignable cause is not identified during Phase I laboratory investigation… Phase II – Production Review (full scale OOS investigation) should be initiated". A total of 21 impurity related OOS were initiated (for products intended for US distribution) from January 2015 to January 2020, with 3 escalated to Phase II. However, deficiencies in (b) (4) were not considered even a contributing factor until an OOT impurity result was reported for (b) (4) batch (b) (4) (OOT Ref No. BP1/OOT/19/011), of an impurity content of (b) (4) % against the finished product specification of NMT (b) (4) (OOT Action Limit of (b) (4) %). Technical Report PEL/TR/BL.14.0625/19/003, established a direct impact of

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intensity and duration of (b) (4) to amount of remnant impurities. However, at the time of this inspection, no historical review had been performed to assess the causal impact of the noted deficiencies in performance, verification and documentation of the (b) (4) during manufacturing operations. All products manufactured for direct or indirect distribution to the US market undergo (b) (4) as part of the manufacturing process.

3. Equipment used in production operations are not adequately qualified. Specifically,

A. During execution of BP/PROD-CQC/17/P/002-OQ, "Protocol for Operational Qualification of (b) (4), installed in (b) (4) ID No. C1S-207B, was qualified using (b) (4) (b) (4) test pieces created from (b) (4) pieces of an (b) (4) removed from (b) (4) ID No. C1B-(b) (4) -02. There is documentation present to ensure the composition of the generated test pieces. Additionally, the acceptance criteria established in the qualification protocol was established as 100% recovery of the trapped (b) (4) specimens. However, the mass of the generated test samples was not weighed prior to being passed through the (b) (4) nor after completion, to ensure 100% recovery. The "Report for Operation Qualification of (b) (4) Report No. BP/PROD-C1C/17/R/002-OQ, approved on August 31st, 2017, relied on visual verification of 100% recovery, to satisfy the acceptance criteria. (b) (4) ID No. C11S-207B and other (b) (4) of similar design, qualified in a similar manner, are used in the production of marketed US API products (b) (4) USP, and (b) (4) USP. Furthermore, these (b) (4) are also proposed for use in support of (b) (4) (b) (4) for (b) (4) drug substance and (b) (4) drug substance. (b) (4) particles have previously been observed during production of (b) (4) Batch No. (b) (4) on (b) (4) (b) (4)

B. No verification was performed during qualification or at any time thereafter, of the HMI fixed recipe operational parameters for (b) (4) for (b) (4). The (b) (4) utilizing the HMI assigned fixed-recipes for operational parameters, are non-dedicated and used interchangeably within the (b) (4) production block, in the manufacture of finished API drug product used in the manufacture of finished drug product, to be distributed to the US market.

C. (b) (4) test pieces used to challenge (b) (4) ID No. C2(b) (4) -01 and C1B-(b) (4) -01, used in the production of (b) (4) USP (b) (4) and (b) (4) USP, are

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not traceable to any certified standard to verify composition.

4. Failure to fulfil the responsibilities of the Quality Control Unit. Specifically,

Review, verification and control of documents involved in the production, testing, analysis, review, release and reject of intermediate and finished API products are deficient. For example,

A. No records are generated or verified with respect to Approval/Quarantine/Reject labels applied to in-n-process, intermediate, or finished API product. Labels are generated using word processing software, labels are not verified for accuracy in regard to Batch No., Inspection Lot No., or Retest Date, prior to being affixed to product containers. Additionally, no reconciliation of generated labels is performed. Similar documentation deficiencies were observed with "Under Test" and "Sample Pack" labels.

B. Master Batch Record documentation were observed to have been reviewed and approved by the Quality Unit, without requiring documentation of critical process parameters. Executed batch records were similarly reviewed, approved with product subsequently released, without documentation of critical process parameters.

C. Multiple copies of forms/log-sheets are generated and provided to various departments. Multiple forms documenting actions during the same time period were observed. Additionally, documents were observed with data entered prior to the documented QA issuance date.

D. The sterility of purchased (b) (4) (Material Code No. (b) (4)) has never been assessed or verified. Supplier qualification was performed, and the report was approved on November 28th, 2018, without ever ensuring that the containers, which are defined as "critical consumables" per SOP No. CQCM/SOP/039, "Receipt, Storage, and Handling of Standard Kits, Endotoxin Test Reagents and Critical Consumables", Effective Date: October 23rd, 2018, are sterile upon receipt.

E. Transportation of Microbiological samples for Identification, per SOP No. CQCM/SOP/038, "Receipt and Transport of Microbiology Samples", Version 02, Effective Date: May 25th, 2018, does not require documentation of the temperature conditions during transport of microbiological ((b) (4) Environmental Monitoring, Cleaning Validation) samples to (b) (4) , for species identification. However, the procedure

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specifies storage of microbiological samples at 2-8°C is required, if not analyzed "immediately".

5. Failure to adequately handle, store and document material movement and status. Specifically,

Material of different status' were observed on January 23rd, 2020 in the (b) (4) storage, (b) (4) and (b) (4) to be comingled. Material Status Placards were observed to incorrectly identify the status of the storage shelf contents. Additionally, inventory records tracking the inward/ outward, sampling and disposition of materials, were observed to be inaccurate. No use of Reject labels was observed in any product despite the requirement of such, per SOP No. (b) (4) /PROD/SOP/003,"Department Functional Procedure", Version 12, effective date: April 4th, 2018.

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